National Advisory Council for Human Genome Research
Concept Clearance for Technology Development RFAs
September 16 - 17, 2019

Purpose:

The purpose of the activities presented in this concept clearance, along with the accompanying concept clearance for a Program Announcement with Special Review Criteria (PAR), is to accelerate innovation, development and early dissemination of genomics technologies. This concept proposes the following activities: 1) reissuing a Request for Applications (RFAs) focused on novel, and potentially transformative approaches for sequencing of DNA and RNA; 2) issuing new RFAs focused on advancing technologies to inexpensively and accurately synthesize specified sequences of nucleic acids at the scale needed for genomics-based research; and 3) issuing a new RFA for a Technology Development Coordinating Center focused on facilitating dissemination of information and technologies, providing opportunities for rapid advances, and enhancing collaborations. The work proposed in these concepts would, if successful, propel and transform genomics, and enable significant advances in both biomedical research and clinical settings.

Background:

A rapid creative destruction and rebirth process of technology advances underlies much of the progress in our understanding, knowledge and capabilities in the field of genomics. The National Human Genome Research Institute (NHGRI) has a unique, deep, and long-standing commitment to fostering genomic technology development. NHGRI's investment in catalyzing the development of new DNA sequencing technologies was a major part of the underlying successes in reaching the '$1000 genome.' In 2015, NHGRI broadened the scope of the technology development program by adding solicitations focused on other genomic technologies and simultaneously reduced the amount of funding for nucleic acid sequencing technology. Specifically, extending beyond sequence per se, these solicitations supported technology development to determine genomic function, gene regulation, chromatin state, nuclear organization, and dynamics of those features in genomes of single cells, or mixed populations of cells. These efforts, which include both traditional research application types (R01 and R21) and small business applications (R43 and R44), were renewed in 2018. NHGRI also accepts investigator-initiated technology development applications that come in under the NIH parent announcements.

Early input into NHGRI strategic planning for a "2020 Vision for Genomics" has revealed strong enthusiasm for the institute continuing to pursue activities that will catalyze the development of a suite of novel genomics technologies. NHGRI remains committed to supporting very novel and high impact work from across the gamut of genomics technology development, particularly technologies that will have a major impact in the next five to seven years. Despite enormous advances, many genomic approaches remain far from achieving the low costs, high quality, and rapid time to results that are needed to generate and utilize comprehensive genomic information in many research applications or in clinical care.

Input from town halls, workshops and other strategic planning forums highlighted two specific areas for NHGRI to foster. First, this is a critical time for NHGRI to increase the investment in the core area of nucleic acid sequencing technologies. Despite the amazing and impactful success of the $1000 genome effort, advances in the field of genomics are still dependent on continued cost reductions, improved long read technologies, and transformative approaches to both DNA and RNA sequencing. Second, there is an emerging need for cheaper and more efficient ways to synthesize nucleic acid sequences. The ability to go from an observational approach of sequencing DNA to a more experimental approach of synthesizing DNA has opened powerful new avenues of genomic applications. Being able to scale activity in this area will be even more transformative. Focused investment in these two areas,

sequencing and synthesis, will stimulate additional sustained technology innovation and development that is foundational to catalyzing advances in genomic science, biomedical research and medicine.

The technology development program of NHGRI consists of a growing set of interrelated efforts. With more recent efforts broadening the program into genomics technologies, the contributing community of researchers has become more complex and diverse, and encompasses a larger breadth of biological, chemical, engineering and physical sciences. The impact of these efforts will benefit from a coordinating center that will enable innovation, opportunities for collaborations across boundaries, and sharing of information, strategies and approaches as the new technologies proceed through a continuum of discovery, development, application and commercialization.

Proposed Scope and Objectives:

This concept proposes technology development in two distinct areas: 1) nucleic acid sequencing, and 2) synthetic nucleic acids, as well as a third activity to create a coordinating center, as described below. Other areas of genomic technology opportunities will be addressed in the companion Genomic Technology Development (PAR) Concept.

As with earlier NHGRI funded technology efforts, applications that are focused on the development of completely novel approaches, or significant refinement of current approaches are sought. Ultimately, the field requires orders of magnitude improvements in efficiency, cost and accuracy for both nucleic acid synthesis and sequencing technologies to be used routinely in research and clinical settings. Additionally, the proposed coordinating center will enhance and expand efforts to support and coordinate technology transfer from developers to users, and promote collaborative, multidisciplinary programs that closely integrate research projects in academic, clinical and commercial laboratories.

1) Nucleic Acid Sequencing (renewal)

- Novel chemistries and instrumentation for DNA and direct RNA sequencing, including:
  - Alternative approaches (e.g., Semiconductor-like sequencers, biological and solid-state nanopores, and new physical methods of sequentially detecting individual bases)
  - Novel methods enabling genome phasing, significantly increasing read lengths, and telomere to telomere sequencing with no unresolved gaps
  - Simultaneous detection of multiple base modifications
  - Technology advances that would enable emerging or novel clinical applications (e.g., order of magnitude changes in turnaround time, and application to clinical samples that cannot be sequenced using current technologies)

2) Synthetic Nucleic Acids (new initiative)

- Innovating technologies and methodologies in nucleic acid synthesis, assembly of larger synthetic nucleic acids, and handling for use in genomics-based applications, including:
  - Significantly increased lengths, multiplexing, and throughput for synthesis at scale
  - More efficient methods for accurate assembly of much longer nucleic acids
  - Substantially reduced costs for including DNA and RNA base modifications
  - New or improved methodologies for specific and high-throughput delivery to biological systems

3) Coordinating Center (new initiative)

- Facilitate collaborations, synthesize findings and disseminate advances
- Promote efforts to benchmark genomics technologies
- Develop a technology transfer resource to facilitate a path to research and clinical utilization
- Provide opportunity funds for promising small-scale work through a rapid infusion of funds for

technology innovation or early development

Relationship to Ongoing Activities:

The proposed initiatives will uniquely address technology development for nucleic acid sequencing and synthetic nucleic acids. Some related applications may also be received through the NIH Parent R01 and R21 announcements. The companion Genomic Technology Development PAR Concept will explicitly exclude work in nucleic acid sequencing and synthetic nucleic acids, as specified in these RFAs. The proposed work is complementary to ongoing technology development activities in other NHGRI programs (e.g., CEGS, GSP and ENCODE).

Commercial interests are actively developing and deploying technologies in each of these areas. To the extent possible, NHGRI will attempt to avoid overlap with those efforts, and leverage opportunities. Support for commercial efforts in these areas will continue to be encouraged via the Small Business Program of NHGRI, through the general omnibus funding opportunity announcements for SBIR R43/R44 and STTR R41/R42.

Mechanism of Support:

1) **Nucleic Acid Sequencing**
   - R01 (Research Project) up to $700,000 direct costs/year; project period of up to 4 years*
   - R21 (Exploratory/Developmental Research) up to $200,000 direct costs/year; maximum of $400,000 for grant; project period of up to 3 years*
   - R43/R44 SBIR Project grant mechanisms
   - Receipt dates for alternating council rounds**
2) **Synthetic Nucleic Acids**
   - Same as Nucleic Acid Sequencing, except R01s will have a project period of up to 3 years
3) **Coordinating Center**
   - U24 (Resource-Related Research Projects--Cooperative Agreements) up to $1,000,000 direct costs; project period of 4 years
   - One receipt date

* The proposed amounts allow for more yearly money than standard; for R21s, the announcements also allow additional time. This flexibility addresses the fact that these are often complex or transdisciplinary projects that require many different and complementary skill sets. The total project budget and duration will vary to match the research proposed.

** The current Novel Nucleic Sequencing Technology Development RFA has only one receipt date per year. More frequent, alternating receipt dates will enable more new applications to be considered across the funding period, faster turnaround of amended applications, and more opportunities for applications that build on previous funding, thereby further accelerating technology innovation and development.

Funding Anticipated:

1) **Nucleic Acid Sequencing**
   - $4,000,000 in total costs/year to fund 4-6 R01 or R21 competing applications/year in FY22-24.
2) **Synthetic Nucleic Acids**
   - $3,000,000 in total costs/year to fund 3-8 R01 or R21 competing applications/year in FY21-23.
3) **Coordinating Center**
   - $1,500,000 total costs/year to fund one U24 from FY21-FY24.

Appendix 1: Mechanism Overview.
Appendix 2: Novel Nucleic Acid Sequencing Technology Development RFA Grants (FY16-FY19).

Appendix 1. Mechanism Overview.

Request for Applications (RFAs)

FOA set	Funding dates	Activity Code(s)	Max award duration	FY19 competing	Requested competing $	Estimated plateau $**
Nucleic Acid Sequencing	FY22-FY24	R01, R21 & R43/R44	4 years	$2.0M*	$4.0M	$13.0M
Synthetic Nucleic Acids	FY21-FY23		3 years	-	$3.0M	$8.1M
Coordinating Center	FY21	U24	4 years	-	$1.5M	$1.5M
Total				**$2.0M**	**$8.5M**	**$22.6M**

* The currently-approved Nucleic Acid Sequencing RFA competing budgetary set-aside for FY19-FY21.

** Maximum total amount invested per year to the three types of RFAs is reached in the final year of funding.

Technology Development (RFAs)

Appendix 2. Novel Nucleic Acid Sequencing Technology Development RFA grants awarded (FY16-FY19).

Grant	PI	Title
R01		
HG005115	Gundlach, Jens*	High Accuracy Nanopore Sequencing
HG009180	Lindsay, Stuart	Recognition Tunneling for Single Molecule RNA Sequencing
HG009186	Wanunu, Meni	Direct picogram DNA and RNA sequencing using nanopore Zero-mode waveguides
HG010053	Akeson, Mark	A Unified Nanopore Platform for Direct Sequencing of Individual Full Length RNA Strands Bearing Modified Nucleotides
HG009188	Collins, Philip	DNA Sequencing Using Single Molecule Electronics
HG002776	Muthukumar, Murugappan*	Computational Design Engine for Accurate and Efficient Sequencing of DNA and RNA
HG009189	Shepard, Kenneth	Enzyme-less DNA base discrimination using solid-state nanopores with high-frequency integrated detection electronics
HG009190	Timp, Winston	Nanopore based profiling of epigenetic state
HG010538	Timp, Winston	Direct nanopore detection of modified RNA to probe structure and dynamics
R21		
HG010108	Kim, Sanggu	High-accuracy, long-range sequencing for HIV-1 genotyping
HG010056	Postma, Hendrik	Improving read length, accuracy, and availability of single-molecule DNA sequencing
HG010055	Tung, Steve	Maximizing Spatial Resolution of DNA Sequencing Using Single Carbon Chain
HG010536	Drndic, Marija	DNA Sequencing with novel 2D FET-nanopore devices
HG010522	Lindsay, Stuart	Conductance Fluctuations: A New Approach to Sequencing?
HG010548	Miga, Karen	Improving throughput of long reads with high consensus base accuracy to resolve repetitive DNAs
HG010543	Niederweis, Michael	Single-chain MspA for nanopore sequencing of DNA
HG009187	Bestor, Timothy	Comprehensive Single Molecule Enhanced Detection of Modified Cytosines in Mammalian Genomes
HG009576	Zhang, Shenglong	Development of LC/MS-Based Direct RNA Sequencing with Concomitant Basecalling and Modification Analysis Capability

*Renewals from previous Sequencing Technology Development RFA.

Technology Development (RFAs)

Appendix 2. Novel Nucleic Acid Sequencing Technology Development RFA grants awarded (FY16-FY19).

Grant	PI	Title
R43		
HG009580	Dapprich, Johannes	Amplification-Free Target Enrichment and Direct Sequencing of Large Chromosomal Segments
HG009184	Schibel, Anna	Achieving Single Nucleotide Resolution to Enable DNA Flossing Through Alpha-Hemolysin
HG009196	Ervin, Eric	Nanopore Enabled Exonuclease Sequencing
HG010051	Kanavarioti, Anastassia	Novel Nanopore-based RNA Sequencing using Nucleobase-specific Tags
HG010058	Mir, Kalim	Super-Resolution Sequencing on a DNA Lattice
HG010551	Nagel, Aaron	Exo-Seq for the single molecule of DNA molecules
HG010527	Schibel, Anna	A Better Mechanism for Controlled Nanopore Translocation
HG009578	Alden, Jonathan	Epigenetic fingerprinting of label-free DNA using a solid-state nanopore
HG009573	Reczek, Elizabeth	Methods to enable direct RNA sequencing without amplification
R44		
HG010049	Ervin, Eric	Exonuclease Epigenetic Sequencing
HG009584	Selvaraj, Siddarth	Commercialization of a low-cost user-friendly DNA preparation kit that produces chromosome-span contiguity from conventional short-read sequencing for a wide range of applications
HG010558	Pratt, Mark	Novel sequencing by synthesis platform to greatly reduce the cost of nucleic acid sequencing